REMARKS

Amendments

Claims 1-21, 25, 26, 28-31 and 37 have been canceled, claims 22, 34 and 36 have been amended. Claim 39 has been withdrawn. Upon entry of the amendment, claims 22-24, 27, 32-36 and 38 will be pending. Support for the amendments to the claims can be found in the specification, for example, on page 6, lines 12-21, in Example 1; the Figures; and in the claims as originally filed.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Rejections

Rejections under 35 U.S.C. § 101

Claims 22-25, 27 and 32-38 were rejected under 35 U.S.C. § 101 as allegedly not being supported by either a specific or substantial asserted utility or a well-established utility. Applicant respectfully traverses the rejection.

Claim 22 as amended is drawn to a transgenic mouse whose genome comprises a null NTTP1 allele. According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . " Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. . .
>
> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)).

The standard for "credible" is defined as:

. . . whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

(MPEP 2107.02, III(B)(emphasis added).

According to the Patent Office's own guidance to Examiners:

Langer and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. [citations omitted] . . . Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false.

Compliance with 35 U.S.C. 101 is a question of fact [citations omitted]. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. . . . To do this, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art.

(MPEP 2107.02, III(A)(emphasis added).

Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts.

Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, of the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101.

(MPEP 2107.02, III(B)(emphasis in original and added).

The Guidelines additionally provide that:

> There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed (citations omitted), and whether the asserted utility appears to contravene established scientific principles and beliefs. (citations omitted). Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." (citations omitted). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)(reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response).

(MPEP 2107.02, VII)(emphasis added).

Thus, according to Patent Office guidelines, a rejection for lack of utility should not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. The present invention satisfies either standard. An assertion of utility is presumed to be true. The burden is on the Examiner to show that one of ordinary skill would find the asserted utility to be false.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined.

According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
> . . .

> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834)(emphasis added)(copy attached). Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice are so well accepted as tools for determining gene function that the director of the NIH Chemical Genomics Center of the National Human Genome Research Institute (among others, including Capecchi, Bradley, Joyner, Nagy and Skarnes) has proposed creating knockout mice for all mouse genes:

> Now that the human and mouse genome sequences are known, attention has turnedto elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (Mus musculus) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti, reeler and obese. The large-scale production and analysis of induced genetic mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
>
> . . .
>
> A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized

and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 921)(emphasis added)(copy attached).

With respect to claims drawn to transgenic mice having a null allele, the following comments from Austin are relevant:

> **Null-reporter alleles should be created**
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.

(p. 922)(emphasis in original, emphasis added).

Research tools such as knockout mice are clearly patentable, as noted by the Patent Office:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function), one that is clearly recognized by those skilled in the art.

For example, according to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)) (copy of relevant pages attached), one of the leading textbooks in the field of molecular biology:

> Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an invaluable tool for investigating gene function on a genomic scale.
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> (p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached), another well respected textbook in the field of genetics:

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.
>
> (p. 508)(emphasis added).

According to Joyner (Gene Targeting: *A Practical Approach*, Oxford University Press 2000) (copy of relevant pages attached),:

> Gene targeting in ES cells offers a powerful approach to study gene function in a mammalian organism.
>
> (preface)(emphasis added).

According to Matise et al. (*Production of Targeted Embryonic Stem Cell Clones* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000)(copy of relevant pages attached):

> The discovery that cloned DNA introduced into tissue culture cells can undergo homologous recombination at specific chromosomal loci has revolutionized our ability to study gene function in cell culture and *in vivo*. . . . Thus, applying gene targeting technology to ES cells in culture affords researchers the opportunity to modify endogenous genes and study their function *in vivo*.
>
> (p. 101)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000) (copy of relevant pages attached):

> Targeted gene mutation in mice represents a new technology that is revolutionizing biomedical research.

> Transgenic and knockout mutations provide an important means for understanding gene function, as well as for developing therapies for genetic diseases.
>
> (p. 1, rear cover)(emphasis added).

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, the claimed invention is useful for a particular purpose. The Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice. Utility of the claimed knockout mouse would be apparent to, and considered credible by, one of skill in the art, as the role of knockout mice in studying any and all of these conditions is both specific and substantial.

The Examiner's rejection is primarily based on the assertion that the phenotype exhibited by the claimed mice is not associated with a disease. The Examiner argues that Applicant's asserted utilities relating to using the claimed mouse as a model for disease or to screen for agents or compounds using the mouse are not substantial because the phenotype is not associated with a disease or condition.

The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proffered by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and

therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*Brana* at 1441, *citing In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly,

the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. As discussed above, the claimed mice have demonstrated specific phenotypes. The acceptance among those of skill in the art of knockout mice demonstrating such properties is clearly demonstrated.

Furthermore, Applicant has provided evidence in the form of numerous scientific references supporting the correlation between the tail suspension test and depression (see the Amendment filed 13 January 2005, particularly pp. 6-7). In light of the acceptance in the art of this test as an indicator of depression, Applicant cannot see how the Examiner can possibly argue that the phenotype is not associated with depression.

Definitive proof that the phenotypes observed in the null mouse would be the same as those observed in humans is not a prerequisite to satisfying the utility requirement. It is enough that the claimed mouse demonstrates a phenotype, relative to a wild type control mouse, and that knockout mice are recognized in the art as models for determining gene function, both in mice and in humans. According to Austin et al.:

> Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
> (p. 921)(emphasis added).

In addition, as pointed out by Doetschman, one clearly skilled in the art, (*Laboratory Animal Science* 49:137-143, 137 (1999)(copy attached), the phenotypes observed in mice do correlate to gene function:

> The conclusions will be that the knockout phenotypes do, in fact, provide accurate information concerning gene function, that we should let the unexpected phenotypes lead us to the specific cell, tissue, organ culture, and whole animal experiments that are relevant to the function of the genes in question, and that the absence of phenotype indicates that we have not discovered where or how to look for a phenotype.
> (emphasis added).

In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption in a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied the initial burden.

The Examiner appears to suggest that the utility of the claimed mice is not substantial because using the mouse for further research is not a "substantial utility." Applicant disagrees.

First, it is wholly untrue that further research is required in order to confirm the utility of the claimed mouse in determining the function of NTTP1. The value of knockout mice in determining gene function is well-established and accepted in the art. This is demonstrated by the references cited above. One skilled in the art is well aware of how to use the mouse to determine the function of NTTP1. The Examiner has failed to provide sufficient factual support for the position that it is more likely than not that a person of skill in the art would doubt that Applicant's asserted utility is specific and substantial, which is the standard for establishing a *prima facie* case. See MPEP § 2107.02, IV.

Second, Applicant is claiming a transgenic mouse, and not a method of treating depression. "The claimed invention is the focus of the assessment of whether an applicant has satisfied the utility requirement." (MPEP 2107.02, I). As established above, the transgenic mouse would clearly be considered useful by a person of skill in the art. That the claimed transgenic mouse can be used in a research setting does not mean that the mouse lacks patentable utility. Further characterization (involving "basic research") of the mouse itself is not necessary in order to confirm its utility in studying the function of the NTTP1 gene.

The section entitled "Substantial Utility" provides:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. . . . the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;

Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, **any reasonable use** that an applicant has identified for the invention that can be viewed as providing a public benefit **should be accepted as sufficient,** at least with regard **to defining a "substantial" utility.**

(MPEP § 2107.01 I)(emphasis added).

The MPEP additionally provides:

Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. **Labels such as** "research tool," "intermediate" or "**for research purposes**" **are not helpful** in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP 2107.01, I)

A use is not substantial where further research is required to identify any use. This is not the case in the present application. Knockout mice have a well-known use in the study of gene function. In the present case, the instant invention does not require further research to establish a utility. Applicant has determined that the NTTP1 gene is associated with depression. No further research is required to establish any use. Whether additional research is required to identify therapeutic agents targeting the NTTP1 gene or to further characterize the function of the NTTP1 gene is irrelevant to whether the claimed invention has satisfied the utility requirement.

In addition to their use in studying gene function, the claimed transgenic mice are useful for studying gene expression. The mice within the scope of the amended claims contain a visible marker such as lacZ. Their use in studying gene expression is clearly recognized by those skilled in the art:

> **Null-reporter alleles should be created**
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normallysupport the expression of that gene.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 922)(emphasis in original; emphasis added)(copy attached). Applicant respectfully reminds the Examiner that a claimed invention need only satisfy one of its stated objectives to satisfy the utility and enablement requirements.

As cited above in Austin, and as is well known to one of ordinary skill, the purpose of expression analysis is to determine where the gene is expressed – a use that is credible, substantial and specific to this mouse.

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the NTTP1 gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying NTTP1 gene function with respect to the cited phenotype and expression analysis, and are therefore useful for a specific practical purpose that would be readily understood and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly made a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific and substantial. (*In re Brana*; MPEP § 2107).

Withdrawal of the rejections is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 22-25, 27, 32-38 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges one skilled in the art would not know how to use the claimed invention because the claimed invention is not supported by either a credible specific and substantial asserted utility or a well established utility for the reasons set forth in the utility rejection.

Applicant respectfully traverses the rejection. The claims as amended are directed to a transgenic mouse comprising a null NTTP1 allele. The claimed invention has a credible specific and substantial utility. This issue has been thoroughly argued above, and it is believed that the claimed invention more than satisfies the utility requirements. Therefore, one skilled in the art would clearly know use to use the invention and could practice the invention without undue experimentation.

The Examiner has also rejected claims 22-25, 27, and 32-38 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Applicant respectfully traverses this rejection.

The rejection is based, in part, on the unpredictability of a phenotype in a transgenic mouse. The Examiner argues that the specification has not taught how to use a transgenic mouse without a phenotype or with a transgene-independent phenotype (e.g. the heterozygous mouse). Applicant respectfully disagrees.

Claim 22 is a composition of matter claim directed to a mouse comprising a null NTTP1 allele. The claims encompass two possibilities: (1) a mouse having a single null allele (heterozygous) and (2) a mouse having two null alleles (homozygous). The specification clearly sets forth how to make and use the claimed mice. The heterozygous mice are useful for breeding homozygous mice and for phenotypic evaluation. The specification and Examples show how to use the mice in phenotypic analyses to determine the function of the gene. A person skilled in the art would clearly know how to use the claimed mouse in this way regardless of their specific phenotypic characterizations. Applicant is unaware of any requirement that a claim to a novel composition of matter recite a property or phenotype.

Any phenotypes associated with the heterozygous and homozygous mice are inherent to the mice. The general rule is that disruption of the coding sequence by a positive selection marker, as taught in the specification, will result in a null allele, which by definition involves ablation of gene function (see, for example, Hasty et al., *Gene Targeting, Principles, and Practice in Mammalian Cells* in Gene Targeting: *A Practical Approach*, ed. Joyner, Oxford University Press 2000, p. 5). Ablation of function is expected to result in the same phenotypic response. Many of the phenotypes, however, will not be associated with genotype and therefore will be the same as a wild-type mouse. Thus, the claimed mice can have a "transgene independent" phenotype.

The Examiner cited Crawley for allegedly teaching that the phenotype of a transgenic mouse is not only the result of the targeted disruption, but could be influenced by genetic background. The Examiner argues that Crawley teaches that not all mouse genetic backgrounds are appropriate for a particular study. Crawley also allegedly teaches that the mouse strains used by Applicant, and commonly used in the generation of knockout mice, are unusual on many standard behavioral paradigms.

Applicant submits that Crawley is not sufficient to support the Examiner's assertions.

Crawley reviews the behavior of several inbred mouse strains in a variety of behavioral tests in an effort to help investigators choose a background strain appropriate for their particular study, or to properly evaluate a phenotype observed in a transgenic mouse. However, contrary to the Examiner's assertions, Crawley does not recommend that investigators discontinue use of any strain, including the C57BL/6 and 129 strains used by Applicant. Crawley states:

> There is no "best" strain that can be recommended across all behavioral paradigms for all null mutations. Rather, the strain is chosen for its predicted sensitivity to the null mutation. High-scoring strains will be ideal to detect a null mutation postulated to reduce the behavioral phenotype; low-scoring strains will be ideal for null mutations postulated to elevate the behavioral phenotype; moderate-scoring strains will be ideal when the effects of the null mutation could go either way.

(emphasis added) (p. 120, last paragraph).

Although Crawley suggests that particular strains are more suitable for the creation of knockout mice to be tested in particular behavioral tests, the article makes no mention of the tail-suspension test or any other model for depression-related behavior, let alone what strain(s) are suitable for these tests. Neither Crawley nor any other reference provided by the Examiner demonstrates that Applicant's choice of background strain was inappropriate or that the ES cell line and background strains differ in their response in the tail-suspension test.

Furthermore, Crawley goes so far as to recommend use of the C57BL/6 strain used by Applicant in many behavioral paradigms ("The best choice of an inbred background on which to explore the impact of a null mutation on learning appears to be C57BL/6"(page 110, paragraph 3) "Strains with poor prepulse inhibition, including C57BL/6J..., can be used to improve prepulse inhibition" (as a model of schizophrenia; page 112, paragraph 6)). Crawley does not go so far as to recommend against a particular strain for any study, but cautions that "the genetic background of the inbred mouse strains must be carefully considered in the interpretation of behavioral phenotypes of knockout mice." (see p. 108). Crawley also states that "[u]nderstanding of the behavioral phenotype of the strain in which a mutation will be studied can avoid overinterpretation of the mutant phenotype." (p. 108).

In no way does Crawley indicate that the use of the 129 and C57BL/6 strains would result in an unreal phenotype in the tail suspension test. Crawley fails to support the Examiner's

position that the tail suspension phenotype in the claimed mouse is a result of anything other than the null NTTP1 allele.

The Examiner argues that the phenotypes observed by Applicant may be the result of compensation by other genes, citing Olsen.

Olsen is clearly unsupportive of the Examiner's position. With respect to GABA genes, Olsen concludes that "the use of mutant and knockout mice has aided understanding of the roles of GAD and GABAR in the intact mammalian organism, with much promise for additional information to come" (p. 91). Even with respect to mice having increased lethality, Olsen states: "[t]he γ2 and β3 subunit knockouts are associated with early postnatal lethality but have nonetheless provided considerable new information about their importance, including relevance to neurodevelopment, synaptogenesis, and possibly human disease. The β3 is a strong candidate for involvement in the epilepsy and other phenotypic attributes of Angelman syndrome, a human genetic disorder characterized by mental retardation, seizures, motor incoordination, and sleep disturbances. The γ2L knockout has allowed direct testing and negation of the selective subunit hypothesis for ethanol modulation of GABAR function. The δ subunit knockout appears to provide information about the function of GABAR in adult cerebellum, dentate gyrus of the hippocampal formation, and the thalamus. GAD_{65}, GABAR β3, and GABAR δ subunit knockouts all exhibit spontaneous seizures, but of different sorts, confirming suspicions that GABAR malfunction might produce epilepsy by more than one mechanism and providing excellent animal models for investigation of the cause of the seizure phenotype." (p. 91-92).

Olsen goes further: "[i]n summary, transgenic and knockout mice have demonstrated that GABA plays a major role in brain development, control of palate formation, and epileptogenesis via multiple mechanisms." (p. 92). It is untenable to cite Olsen as standing for the proposition that knockout mice do not have a well-accepted use.

In the present case, the claimed NTTP1 null mouse in fact demonstrated a phenotype. Olsen would agree that such mice are clearly useful, thus enabling a person skilled in the art to use the mice without undue experimentation.

Regardless, Applicant submits that the issue of compensation is not relevant to whether the claimed mouse meets the enablement requirement. Whether the phenotypes are a direct or indirect result of the null allele is irrelevant as a drug targeting the gene or gene product would have the same effect - directly or indirectly. Whether other genes or pathways attempt to

compensate for the phenotype is not relevant to whether the mouse has a phenotype. In fact, compensation for a phenotype would be more likely to mask a phenotype. The Examiner's position is based on conjecture, and is not sufficient to demonstrate that one skilled in the art would not be enabled to use the claimed mouse. The Examiner has provided no evidence supporting involvement of genes unrelated to NTTP1 in the recited phenotypes.

Applicant submits that one skilled in the art would have been enabled by the specification to make and use the mouse as presently claimed.

Withdrawal of the rejection is respectfully requested.

The Examiner has also rejected the claims under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Applicant respectfully traverses the rejection.

The Examiner argues that Applicant did not demonstrate possession of the genera of a null allele comprising "exogenous DNA" or a "visible marker". The Examiner asserts that the specification does not disclose a knockout mouse comprising a null allele comprising exogenous DNA or a visible marker, and therefore these limitations constitute new matter. Applicant respectfully disagrees with the Examiner's conclusions. However, the amendments to the claims overcome the rejection. Applicant submits that the claims as amended do not constitute new matter.

Withdrawal of the rejection is respectfully requested.

Double Patenting

The Examiner has indicated that should claim 25 be found allowable, claim 32 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. Claim 25 has been canceled.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **502775**.

Respectfully submitted,

6-22-05

Date

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